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# Serum albumin and C-reactive protein/albumin ratio in community-acquired pneumonia

## Toplum kökenli pnömönide serum albümin ve CRP/albümin oranının hastalık seyrine etkisi

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## ABSTRACT

**Introduction:** Community-acquired pneumonia (CAP) is a common type of respiratory tract infections with high morbidity and mortality. Prognostic role of CRP/Albumin ratio in CAP patients still is unknown. The aim of this study was to investigate the role the CRP/albumin ratio in predicting 30-day mortality and ICU requirement in hospitalized patients with CAP.

**Material and Method:** The study included patients with CAP.Clinical records and plain radiographic images of the patients were retrieved from hospital database and were reviewed for each patient.

**Results:** The 179 CAP patients who were hospitalized were included. CRP level and the CRP/albumin ratio were found to have no significant effect on mortality and ICU requirement (p=0.728, p=0.232, and p=0.110, respectively), whereas low albumin level was associated with high mortality and ICU requirement (p<0.001 for both).

**Conclusion:** Increased albumin concentration was associated with a lower risk of 30-day mortality. The CRP/albumin ratio was found to have no significant role in predicting short-term mortality and morbidity in CAP patients. Further large-scale, multicenter studies are needed to investigate the prognostic value of the CRP/albumin ratio in predicting long-term prognosis in CAP patients.

**Keywords:** Community-acquired pneumonia, biomarkers, mortality, prognosis

## ÖZ

**Amaç:** Toplum kökenli pnömöni (TKP) solunum yolu enfeksiyonları içinde yüksek mortalite ve morbiditeye sahiptir. Tanı, tedavi, prognoz takibinde çeşitli biokimyasal markerlar kullanılmaktadır. CRP, albümin rutin uygulamada sıklıkla kullanılan biokimyasal markerlardır. İnflamasyon temellli CRP/albümin oranı çeşitli hastalıklarda prognoz tahmininde kullanılmaktadır. Bu çalışmanın amacı TKP nedeniyle hastaneye yatırılan CRP/albümin oranının 30 günlük mortalite tahminindeki rolünü belirlemekti. Çalışmanın ikincil sonlanım noktası ise yoğun bakım ihtiyacı idi.

**Gereç ve Yöntem:** Göğüs hastalıkları ve yoğun bakım servisine yatırılan TKP'li hastalar çalışmaya dahil edildi. Retrospektif olarak hasta dosyaları, radyolojik incelemeleri ve laboratuvar bulguları tarandı.

**Bulgular**: Yüz (%55,9)'ü göğüs hastalıkları servisinde 79'u yoğun bakımda yatmakta olan 179 TKP'li hasta çalışmaya dahil edildi. Hastaların yaş ortalaması 72,027±12,88 yıldı; %61,5'i erkek, %38,5'i kadındı. CRP değeri ve CRP/albümin oranı 30 günlük mortalite ve yoğun bakım ihtiyacını tahmin etmede anlamlı bulunmazken (sırasıyla p:0,728, p:0,232, p:0,110), düşük albümin değerlerinin mortalite ve yoğun bakım ihtiyacı riskini anlamlı derecede artırdığı bulundu (p<0,001, p<0,001). CURB-65, PSI ve albümin 30 günlük mortalite ve yoğun bakım ihtiyacını tespit etmede anlamlı bulunan değişkenlerdir.

**Sonuç:** Albümin değerinin yüksek olması TKP'de 30 günlük mortalite ve yoğun bakım ihtiyacı riskini azaltmaktadır. CRP, CRP/albümin oranının TKP'de kısa dönem mortalite ve morbiditeyi tahmin edememektedir. TKP'li hastalarda serum albümin, CRP düzeyleri ve CRP/albümin oranının uzun dönem prognozu tahmin gücünü ortaya koymak için geniş kohortlarda, çok merkezli çalışmalara ihtiyaç vardır.

**Anahtar Kelimeler:** Toplum kökenli pnömöni, biyomarkerlar, mortalite, prognoz

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## INTRODUCTION

Community-acquired pneumonia (CAP) is a common type of respiratory tract infections with high morbidity and mortality. CAPis acquired in the community during daily life activities.Chest radiography is commonly used in the diagnosis of CAP patients,often supported bybiochemical parameters such as C-reactive protein (CRP) which is an acute phase protein produced by liver (1,2).

In infection, the decreased albumin synthesis from livermay alter the pharmacokinetic effects of antimicrobial therapies, thereby leading to decreased achievement of pharmacodynamic targets for antimicrobial agents, ultimately resulting in suboptimal treatment. On the other hand, albumin level has also been associated with mortality in diseases including CAP (3,4). CRP/albumin ratio, as a novel parameter, has been shown to be more accurate than albumin and CRP alone in predicting overall prognosis of certain clinical conditions (5,6).

The present study was designed to investigate the role of CRP and albumin levels and the CRP/albumin ratio in predicting 30-day mortality and the requirement of intensive care unit (ICU) admission in hospitalized patients with CAP.

## MATERIAL AND METHOD

The retrospective study included a total of 179 patients diagnosed with CAP that were followed up in ICU and in inpatient clinic between 2012 and 2018. This study approved by Ufuk University Non-Interventional Clinical Researches Ethics Committee (Date: 07.03.2019, Decision No: 20190703/10).

Clinical records and plain radiographic images of the patients were retrieved from hospital database. Patients that were grouped based on the Confusion Urea Respiratory Rate Blood Pressure-65 (CURB-65) and pneumonia severity index (PSI) scores, clinically and radiologically diagnosed with CAP, initiated on a therapy based on national or international guidelines, and were followed up for a minimum of one month, and patients that underwent chest radiography within the first 24 h after admission, underwent complete blood count and biochemical analysis including CRP and albumin were included to the study (1,7-9).The guidelines recommend ICU admission in the presence of at least one major criterion or three minor criteria (7-9).Exclusion criteria were as follows: <18 years, pregnancy, active infection other than CAP, hospital-acquired pneumonia and ventilator-associated pneumonia, myocardial infarction, chronic kidney disease, malignancies, a history of connective tissue disease, and immunosuppressive drug use within one month. Based on the chest radiographs, the patients were divided as having bilateral, unilateral, reticular,and bronchoalveolar infiltration. For the patients hospitalized in ICU, the Acute Physiology and Chronic Health Evaluation II (APACHE-II) scores and the predicted mortality rates were recorded retrospectively (10).Based on arterial blood gas analysis at room air performed on admission, patients with partial pressure of oxygen ($PaO_2$) <60 mmHg and partial pressure of carbon dioxide ($PaCO_2$) <45 mmHg were accepted as hypoxic and patients with $PaO_2$<60 mmHg and $PaCO_2$>45 mmHg were accepted ashaving hypercapnic respiratory failure. CRP and albumin levels were measured spectrophotometrically using an Abbott Architect C8000 apparatus. The normal reference ranges used for CRP and albumin levels were 0.01-5 mg/L and 2.5-5 g/dL, respectively.

### Statistical Analysis

Statistical analyses were performed using SPSS for Windows version 23.0 (IBM SPSS Inc., Armonk, NY, USA). Descriptives were expressed as frequencies, percentages, mean±standard deviation (SD), and median (minimum-maximum). Normal distribution of data was tested using Kolmogorov-Smirnov and Shapiro Wilk tests. Homogeneity of variances was tested by Levene's test. Continuous variables were compared using Student's t-test or Mann-Whitney U test and categorical variables were compared using Chi-square test. Correlations between variables were determined using Spearman's Rank Correlation Coefficient. Univariate and multivariate analyses of logistic regression were performed to determine the factors affecting ICU requirement, and mortality ROC curves were constructed to compare the diagnostic values of parameters including CRP/albumin ratio, PSI, CURB-65, APACHE II, predicted mortality rate, and ICU requirement. Sensitivity, specificity and area under the ROC curve (AUC) were determined based on 95% confidence interval (CI). A p value of <0.05 was considered significant.

## RESULTS

The patients included 110 (61.5%) men and 69 (38.5%) women with a mean age of 72.027±12.88 years.Of these, 131 (73.2%) patients were present with comorbidities. **Table 1** presents the demographic characteristics of the patients.

All the patients (100%) had hypoxic respiratory failure and 32 (17.9%) patients had hypercapnic respiratory failure. The one-month mortality rate was 31.3%. **Table 2** presents the radiological findings, lengths of ICU stay,

mortality rates, and CURB-65 and PSI scores. In the 79 patients admitted to ICU, mean APACHE-II score was 28.25±6.73and the mean predicted mortality rate was 60.96%±21.19%.

The CRP level was higher in 176 (98.3%) and lower in 3 (1.7%) patients compared to the normal range. The albumin level was normal in 127 (70.9%) and higher in 52 (29.1%) patients compared to the normal range. Mean CRP and albumin levels were 111.18±95.32 mg/L and 2.9±0.69 g/L, respectively, and the mean CRP/albumin ratio was 42.29±39.8. In the multivariate logistic regression analysis, PSI, CURB-65, and serum albumin level were found to be effective factors for mortality and ICU requirement (**Table 3**).

In the ROC analysis, PSI score, CURB-65 score, and albumin level were found to be significant predictors of mortality and ICU requirement (p<0.001 for both) (**Figure 1, 2**) and increased albumin level were found to be protective factors for mortality and ICU requirement. However, the CRP/albumin ratio was found to have no significant effect on mortality and ICU requirement (p=0.232 and p=0.110, respectively).

The CRP/albumin ratio was significantly lower in PSI I-III patients compared to PSI IV-V patients (33.84±32.35 vs. 49.132 ±43.911;p=0.014); however, no significant difference was found between patients with a CURB-65 score ≤2 and >2 with regard to the CRP/albumin ratio (40.244±34.937 vs. 43.186±41.832; p=0.883). On the other hand, the CRP/albumin ratio was significantly higher in patients detected with bilateral infiltrates compared to patients detected with unilateral infiltrates on chest radiography (51.863±42.896 vs. 36.438±36.766;p=0.007).In contrast, no significant difference was found between patients with reticular infiltrates compared to patients bronchoalveolar infiltrates with regard to the CRP/albumin ratio (43.488±41.587 and 41.620± 38.921, respectively) (p=0.935).

**Table 1.** Demographic characteristics of the study group

| **Age (years)** | **Mean±SD** | **Median (D.Gen)** | **N** |
|---|---|---|---|
| | 72.027±12.88 | 75 (74) | 179 |
| **Variables** | | **N** | **%** |
| Gender | Male | 110 | 61.5 |
| | Female | 69 | 38.5 |
| Comorbidities | No | 48 | 26.8 |
| | Yes | 131 | 73.2 |
| COPD | No | 117 | 65.4 |
| | Yes | 62 | 34.6 |
| DM | No | 137 | 76.5 |
| | Yes | 42 | 23.5 |
| CAD | No | 136 | 76 |
| | Yes | 43 | 24 |
| CKD | No | 168 | 65.4 |
| | Yes | 11 | 6.1 |

COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, CAD: Coronary artery disease, CKD: Chronic kidney disease

**Table 2.** Clinical characteristics of the patients

| **Variables** | | **N** | **%** |
|---|---|---|---|
| CURB-65 | 2 | 54 | 30.2 |
| | 3 | 75 | 41.9 |
| | 4 | 32 | 17.9 |
| | 5 | 18 | 10.1 |
| PSI | 2 | 23 | 12.8 |
| | 3 | 57 | 31.8 |
| | 4 | 55 | 30.7 |
| | 5 | 44 | 24.6 |
| ICU admission | No | 100 | 55.9 |
| | Yes | 79 | 44.1 |
| Mortality | No | 123 | 68.7 |
| | Yes | 56 | 31.3 |
| Infiltration | Unilateral | 111 | 62 |
| | Bilateral | 65 | 38 |
| Infiltration type | Bronchoalveolar | 114 | 63.7 |
| | Reticular | 65 | 36.3 |
| NIV | No | 147 | 82.1 |
| | Yes | 32 | 17.9 |
| IMV | No | 109 | 60.9 |
| | Yes | 70 | 39.1 |
| WBC | Normal | 66 | 37.9 |
| | High | 108 | 62.1 |
| HB/HCT | Low | 69 | 38.5 |
| | Normal | 101 | 56.4 |
| | High | 0 | 5 |
| Creatinine | Low | 0 | 0 |
| | Normal | 139 | 77.7 |
| | High | 40 | 22.3 |
| BUN | Low | 0 | 0 |
| | Normal | 139 | 77.7 |
| | High | 40 | 22.3 |

NIV: Noninvasive ventilation, IMV: Invasive mechanical ventilation, ICU: Intensive care unit, CURB-65: Confusion Urea Respiratory Rate Blood Pressure-65, PSI: Pneumonia Severity Index, WBC: White blood cell, BUN: Blood urea nitrogen, HB: Hemoglobin, HCT: Hematocrit

**Table 3.** Multivariate analysis of factors affecting 30-day mortality (I) and ICU requirement (II)

| **Variables** | **B** | | **Standard Error** | | **O.R.** | | **95% CI** | | | | **p** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | **Lower bound** | | **Upper bound** | | | |
| | **I** | **II** | **I** | **II** | **I** | **II** | **I** | **II** | **I** | **II** | **I** | **II** |
| PSI score | | | | | | | | | | | | |
| (3) | -0.978 | 0.086 | 1.344 | 1.199 | 0.376 | 1.090 | 0.027 | 0.104 | 5.236 | 11.437 | 0.467 | 0.943 |
| (4) | 1.192 | 1.818 | 1.200 | 1.151 | 3.294 | 6.158 | 0.313 | 0.645 | 34.626 | 58.786 | 0.321 | 0.114 |
| (5) | 4.127 | 4.127 | 1.307 | 1.557 | 11.543 | 62.009 | 1.010 | 2.930 | 149.638 | 1312.130 | 0.041 | 0.008 |
| CURB-65 score | | | | | | | | | | | | |
| (3) | 1.086 | 1.086 | 0.887 | 0.657 | 3.587 | 2.964 | 0.631 | 0.817 | 20.405 | 10.747 | 0.150 | 0.098 |
| (4) | 2.697 | 2.697 | 0.977 | 0.921 | 14.120 | 14.837 | 2.079 | 2.441 | 95.887 | 90.185 | 0.007 | 0.003 |
| (5) | 1.504 | 1.504 | 1.199 | 1.623 | 12.520 | 4.502 | 1.193 | 0.187 | 131.390 | 108.378 | 0.035 | 0.354 |
| Albumin* | 1.177 | 1.177 | 0.323 | 0.459 | 4.694 | 3.246 | 2.493 | 1.319 | 8.849 | 8.000 | <0.001 | 0.010 |

PSI:Pneumonia Severity Index, CURB-65: Confusion Urea Respiratory Rate Blood Pressure-65, ICU: Intensive care unit, *Albumin was found to be a protective factor. Lower albumin levels indicate a higher risk.

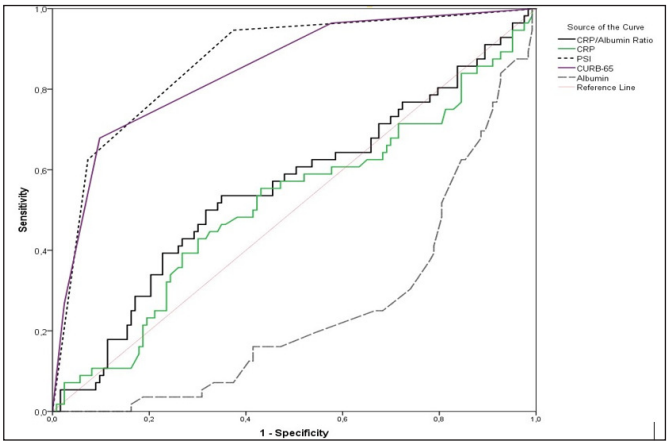


**Figure 1.** Predictive value of CRP/albumin ratio, PSI, CURB-65, CRP, and albumin for mortality

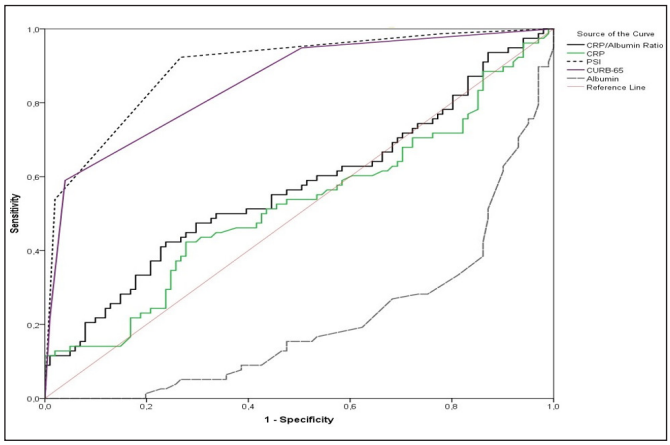


**Figure 2.** Predictive value of CRP/albumin ratio, PSI, CURB-65, CRP, and albumin for ICU requirement

## DISCUSSION

CAP is a significant cause of mortality and morbidity. Despite the recent advancements in treatment methods, CAP still has high complication and mortality rates (8). Similarly, despite optimal treatments, the 30-day mortality rate is 10-12% (11). In the present study, the patients had a higher mortality rate (31.3%) compared to those reported in the literature, which could be attributed to the inclusion of patients hospitalized in both the general ward and ICU and to the high mean age of the patients.

The severity of CAP can be assessed by numerous scoring systems such as PSI and CURB-65 and also by inflammatory markers including CRP, PCT, and albumin (1,12). CRP and albumin, in particular, are commonly used in the evaluation of critical patients (13).

Serum albumin level which is a sensitive indicator of patients' nutritional status is closely associated with mortality in infection-related diseases (14). In the elderly population, low albumin levels on admission are associated with high mortality (15).Charles et al. (16) reported that albumin level was an independent risk factor for vasopressor support and mechanical ventilation and ICU requirement. Another study found that hypoalbuminemia was a significant predictor of mortality in patients with sepsis and septic shock associated with CAP (14). Similarly, in our study, increased serum albumin level was found to be a protective factor for mortality and ICU requirement ($p<0.01$ for both).

In the presence of an infection or inflammation, CRP level increases by about 6 h and peaks at around 48 h (2,17-18). In CAP patients, however, the prognostic value of serum CRP level remains controversial. Lee et al. (12) found that CRP and albumin were independently associated with 28-day mortality when combined with a PSI score >3. Charles et al. (16) found that the failure of CRP to fall by 50% or more within 4 days of admission was an independent risk factor for worse outcomes. Similarly, Nair et al. (19) found a significant association betweena decrease of less than 25% in CRP levels at the second day and mortality in hospitalized patients with severe CAP.

On the other hand, Lee et al. (12) also noted that baseline CRP and albumin levels were significant independent factors for 28-day mortality and that low albumin and high CRP levels were associated with high mortality in hospitalized patients with severe CAP. In our study, although baseline CRP level was not found as a significant factor for predicting mortality and ICU requirement, baseline albumin level had a significant prognostic value in hospitalized patients with CAP, as consistent with the study by Lee et al. (12). This finding could be attributed to the fact the CRP levels in our patients were measured only within the first 24 h after admission and, unlike in previous studies, no serial measurement was performed (2,12,19).

Literature indicates that CRP, albumin, or CRP/albumin ratio can be used as a useful prognostic factor for inflammatory or nutritional status and the CRP/albumin ratio, in particular, can be a strong indicator of inflammatory response (17). A previous study evaluated patients admitted to the emergency department who were older than 65 years and reported that high-sensitivity CRP/albumin ratio was associated with all-cause mortality. Although the authors did not evaluate the scores, changes in mental state, and vital findings of the patients, the causes of mortality were examined in detail (15). Another study evaluated patients admitted to ICU and found that the CRP/albumin ratio was an independent risk factor for 30-day and 12-month mortality. In the same study, the cut-off values for 30-day and 12-month mortality were 1.58 and 1.75, respectively (13). Kim et al. (14) evaluated patients with sepsis and septic shock and suggested that the CRP/albumin ratio could be used for predicting 3-month mortality. The

authors calculated the CRP/albumin ratio based on serially measured CRP levels (14). The present study is the first study in the literature to investigate the prognostic value of the CRP/albumin ratio and to show that baseline CRP/albumin levels are not significant predictors of one-month mortality and ICU requirement in hospitalized patients with CAP. Nevertheless, we could not compare this finding with literature data since, to the best of our knowledge, there has been no study investigating the prognostic value of CRP/albumin ratio for mortality in CAP patients. It is commonly known that there is no standard time interval for the measurement of albumin levels and a single measurement is often adequate for the analysis. However, it is recommended that CRP levels should be measured at appropriate time intervals by serial measurements. In our study, the CRP/albumin ratio was found to have no significant prognostic value for mortality in CAP patients, which could be attributed to the single measurement of CRP levels performed within the first 24 h after admission.

Both PSI and CURB-65 scores are used in the treatment and management of CAP, particularly in making decisions related to outpatient, inpatient, and ICU hospitalization and predicting disease severity and prognosis. In both of these scoring systems, higher scores indicate increased mortality and disease severity (20). Literature also indicates that these two methods have a role in predicting short-term mortality in CAP patients (21). In the study by Lee et al. (12), the CRP/albumin ratio was correlated with PSI scores in predicting mortality although it showed no correlation with CURB-65 scores. Similarly, in our study, no significant difference was found between the patients with low and high CURB-65 scores with regard to the CRP/albumin ratio although the CRP/albumin ratio was significantly higher in patients with high PSI scores compared to patients with low PSI scores.

Pneumonia may present with a wide variety of radiological patterns on chest radiography (22,23). A previous study evaluated the radiological features of CAP and detected alveolar opacities, interstitial opacities, and borderline diffuse infiltrates. This wide variety of features was attributed to advanced age of the patients and the underlying chronic cardiorespiratory diseases (21). Additionally, it is also suggested that the radiological pattern of CAP may vary according to the cause of pneumonia (24, 25).In the present study, all the radiographic examinations were performed by a chest specialist (D.H). However, as the study had a retrospective design, no microbiological sampling that could lead to differences was performed during radiographic examinations. On the other hand, the CRP/albumin ratio was significantly higher in patients that were radiologically detected with bilateral infiltrates, which could be ascribed to the greater number of ICU patients with high APACHE-II scores.

Our study was limited in several ways. First, clinical data of patients were retrieved from electronic databases as the study had a retrospective design. Second, the results of the study may not represent all the CAP patients as the study was a single-center study and only included hospitalized patients. Third, no information was available regarding the specific causes of death in the nonsurviving patients and the mortality records were limited to a one-month period. Finally, no analysis was performed for microbiological factors that could have a significant role in the severity of pneumonia.

## CONCLUSION

The CAP that requires hospitalization or ICU admission is a significant cause of morbidity and mortality. In the present study, albumin level as well as PSI and CURB-65 scores had a significant predictive value for mortality and ICU requirement in CAP patients while CRP and the CRP/albumin ratio had no significant role in predicting the prognosis. Further prospective, multicenter studies performing microbiological analyses and serial CRP measurements are needed to investigate the prognostic value of the CRP/albumin ratio in predicting long-term prognosis in CAP patients.

## ETHICAL DECLARATIONS

**Ethics Committee Approval:** Ethics committee approval was received for this study from the Clinical Trials Ethics Committee of Ufuk University Non-Interventional Clinical Research approved by the Ethics Committee (Date: 07.03.2019, Decision No: 20190703/10).

**Informed Consent:** Because the study was designed retrospectively, no written informed consent form was obtained from patients.

**Referee Evaluation Process:** Externally peer-reviewed.

**Conflict of Interest Statement:** The authors have no conflicts of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

**Author Contributions:** All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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